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THE DIAGNOSTIC AND PROGNOSTIC VALUE OF THE LEUCOPENIA OF CACHEXIAL FEVER AND KALA-AZAR

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large and forcible in the fifth interspace 1½ in. outside the nipple line. The heart's dullness extended 2 in. to the right of the middle line. There was a loud, long systolic murmur—heard at all the areas, loudest at the mitral. She was prescribed a mixture containing tincture of digitalis and tincture of iron, 5 minims of each, three times a day. On November 31st her pulse was observed to be irregular, and a tracing showed a good example of the pulsus alternans (Figs. 8 and 9).

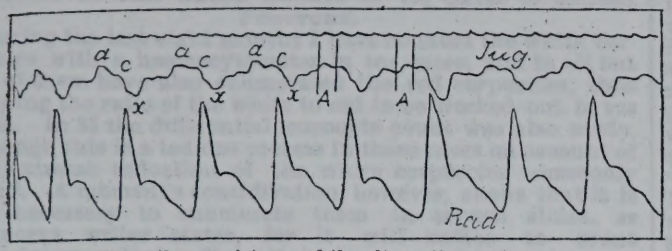

Fig. 11.—Shows the persistence of the alternating action in the radial pulse with marked slowing of the rate, and with no apparent effect on the auricle or on conductivity.

From this date the patient steadily improved. On November 3rd the tracing, Fig. 10, was taken. By November 8th she felt very well, the pulse being slower and fuller, and the jugular pulse much smaller, though a slight alternating rhythm is still observable in the radial pulse (Fig. 11). By the 14th all signs of the jugular pulse and of the pulsus alternans had disappeared, the heart's dullness being greatly diminished and the patient felt much better. Since that date she has had several slight relapses, and though the digitalis has been pushed I never got so marked an alternating rhythm as in these tracings, though after long use of the drug I occasionally detected a slight form of this arrhythmia.

In the jugular tracing of Figs. 9 and 11 there is, again, no sign of conductivity being affected, and it should be noted that, so far as one can judge, the arrhythmia did not appear to affect the auricle. Fig. 10 is of interest. The first part of the tracing shows a slight alternating action with the pulse beats occurring at regular intervals till the beats marked 1-4 occur at slightly more rapid rate, and these beats correspond in size to the smaller beats in the first part of the tracing. This diminution in size is manifestly due to the fact that contractility has not had time to recover. After the fourth small beat there is a pause longer than usual, followed by the largest beat in the tracing. This large beat is manifestly due to the fact that the contractility has had more time for recovery by reason of the long pause after the preceding small beat. The exhaustion after the large wave results in a small wave followed by a larger, and here is apparently the beginning of a period of alternating pulse beats (unfortunately the tracing was stopped here). Hoffmann and Wenckebach have particularly referred to this manner of starting the alternation.

I am inclined to think that there may be found a means of estimating the condition of the function of contractility by noting what effect a change in the period of rest has upon the size and character of the succeeding pulse beat. In a future paper I shall demonstrate this method with more fullness.

This depression of contractility is not common in cases where the auricle is active. From among a large number of observations I have only found three or four instances, and I might have had some doubt in attributing the effect to digitalis were it not that in cases of ventricular rhythm the effect is much more pronounced, and I hope to demonstrate how a depressed condition of contractility in cases with ventricular rhythm can be connected with a similar depression in cases with the auricular or normal rhythm. Furthermore, the following experimental observations demonstrate the justness of the interpretation given above.

Since I wrote this description of the effects of digitalis in contractility, Professor H. E. Hering has sent me the results of some experimental work done in his laboratory at Prague. In one paper Pletnew describes the effect of electric stimulation on the hearts of rabbits under the influence of medicinal doses of digitalis. The drug was carefully pushed, and in two instances, of which he gives tracings, the digitalis produced an alternating effect on the contraction of the heart. It will be seen in Fig. 12 that the arrhythmia is a good example of the alternating action of the ventricle and is in perfect agreement with the results I have just described in the human heart. These tracings also confirm in a most striking manner Wenckebach's description of the nature of the pulsus alternans. By careful measurement of the events in Fig. 12 it will be seen that the starting of the V_s is perfectly regular, but that systole of the lesser beat is distinctly shorter in duration, so that the period of rest after the short beat is distinctly longer than after the large beat. Wenckebach has further pointed out that a beat may drop out from exhaustion of the function of contractility, and the missed beat at x Fig. 12, is due to this cause. The preceding beat is very small and shows the exhaustion is increasing. There is no beat following the auricular systole a'. It might be said that the missing of a beat was due to the depression of conductivity, so that the stimulus failed to reach the ventricle from the auricle; but I have already shown that when digitalis affects conductivity so as to produce a ventricular intermission, that the time between A_s and V_s gradually lengthens, and that the V_s succeeding the pause occurs at a shorter interval after the A_s. By careful measurement it will be noted that conductivity is not in the least affected at any period here, the interval between A_s and V_s being a constant one. The V_s after the pause is the longest and largest in the series, and confirms the explanation I gave for the large beat in Fig. 10. These tracings also confirm the facts shown in my tracings that it is only the contractility of the ventricular fibres that are affected by medicinal doses, for the auricle manifests no corresponding arrhythmia.

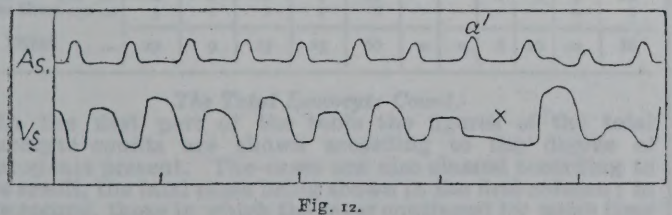

Fig. 12.

Another striking fact brought out by these experiments of Pletnew is that in no instance is there shown any affection of conductivity, affording therefore a support to the statement I have made that digitalis only affects conductivity when this function has been previously damaged. The fact that contractility was affected in the two instances cited suggests the possibility that that function was previously damaged, it might have been during the performance of the experiments. (In another of Pletnew's tracings, Fig. 17, he produced artificially an extra systole, after which there was a prolonged pause followed by a large and prolonged systole, and this started the alternating action in the manner referred to in describing Fig. 10.)

THE DIAGNOSTIC AND PROGNOSTIC VALUE OF THE LEUCOPENIA OF CACHEXIAL FEVER AND KALA-AZAR,

AND ITS TREATMENT BY QUININE AND BONE MARROW.

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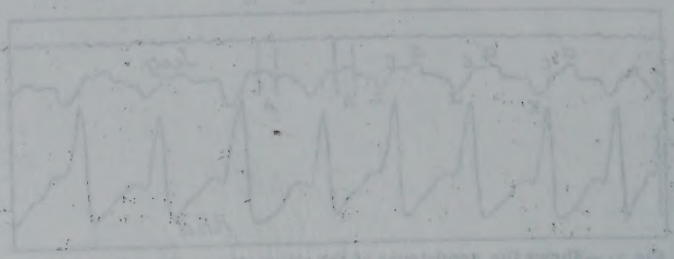
In a paper read before the Oxford meeting of the British Medical Association I drew special attention to the marked degree of leucopenia in cachexial fever and kala-azar, and suggested that it might prove to be of diagnostic value. Further experience has convinced me that this is the case, and I propose to set forth the evidence in favour of this view in the present paper, as it is clearly a matter of the greatest practical importance if even a large proportion of cases of this disease can be correctly inferred from a simple examination of the finger blood, instead of the much more serious operation of spleen puncture; for although the latter method can, with due precautions, be safely performed in the great majority of cases, yet not infrequently the coagulability of the blood is so reduced in cachexial fever as to render it highly inadvisable to puncture the spleen. This is the case mainly in very anaemic subjects, and those who have suffered from various forms of haemorrhage, petechial or otherwise, in some of whom I have found the coagulability of the blood to be considerably reduced, and in such cases I estimate the coagulability first by means of Wright's instrument, and only puncture the spleen if the blood clots within five minutes or less. A fine hypodermic needle should be used.

Nomenclature.

I have retained the name of "cachexial" fever for the endemic form of the disease, so common in Bengal and Madras, until the precise nature of the flagellated protozoal parasite, whose development from the Leishman bodies I have described and figured elsewhere,[1] is exactly determined and named, as it appears to me to be less objectionable than the other names so far suggested. Thus, "tropical splenomegaly" does not cover all cases, as Donovan mentions three in which the spleen was not enlarged, and I have obtained the parasite in several cases in which the organ only extended an inch or so below the costal margin, and have watched a typical case of the disease, showing both the double remittent type of fever described in my last paper, and also the blood changes about to be described, in very marked degree, and during several months before his death the spleen was never large enough to be safely punctured below the ribs. The term "malarial cachexia of India" recently suggested is open to the still



graver objections that the disease is neither malarial nor is it confined to India, while I shall show presently true malarial cachexia does occur in this country. I propose to adopt Colonel Bruce's suggestion to call the spleen form of the new parasite by the name of Leishman alone for sake of brevity.

ANALYSIS OF THE BLOOD COUNTS IN 104 CASES OF SPLEEN PUNCTURE.

During the last eight months I have counted the white corpuscles with a haemocytometer in 104 cases, and in all but two of them have also enumerated the red corpuscles, thus allowing the ratio of the white to red to be worked out in 102 cases. In 88 the differential leucocyte count was also made, although this is a tedious process in these cases on account of the extreme reduction of the white corpuscles commonly found. A moment's consideration, however, shows that it is not necessary to enumerate them in several slides, as a recent writer states, for it will suffice to count all in a single film if they amount to two or three hundred, for there is no reason to suppose that they will be in different proportions in one drop of blood from that which obtains in the next drop, while owing to their small numbers they will be so widely distributed among the red corpuscles that the examination of a large film will give a correct estimation. From the total and differential counts of the leucocytes the total number of polynuclears can be estimated, the extreme reduction in which has been found to be a very important diagnostic point in cachexial fever. The three sets of data just mentioned have been embodied in Table I, so as to allow the variations met with to be readily studied, those cases in which Leishman bodies were obtained by spleen puncture during life, or in two cases after death, being contrasted with those in which negative results were obtained. Malarial parasites were found either in the spleen or in the peripheral blood in several of the latter, while the rest gave negative results.

TABLE I.—*Leucocyte Counts in 104 Spleen Puncture Cases.*

PART I.—Total Leucocyte Counts in 104 Spleen Puncture Cases.

	Leishman Bodies in Spleen Blood.					Leishman Bodies not found in Spleen Blood.					Grand Total
	Died.	Worse.	Doubtful.	Improved.	Total.	Died.	Worse.	Doubtful.	Improved.	Total.	
Over 6,000 ...	—	—	—	—	0	—	—	3	4	7	7
+4,000 to 6,000...	2	—	—	—	2	—	—	—	4	4	6
+3,000 to 4,000...	—	—	1	1	2	—	—	1	3	4	6
+2,000 to 3,020...	2	1	4	10	17	—	—	—	6	6	23
+1,000 to 2,000...	5	4	6	8	23	—	—	2	2	4	27
1,000 and less ...	9	5	9	9	32	—	—	—	3	3	35
Total ...	18	10	20	28	76	0	0	6	22	28	104

PART II.—Ratio of White Corpuscles to Red in 102 Cases.

+1-750	2	—	1	—	3	—	—	4	6	10	13
1-750 to 1-1,000 ...	1	—	2	4	7	—	—	—	4	4	11
1-1,000 to 1-2,000	1	1	7	4	13	—	—	1	4	5	18
1-1,500 to 1-2,000	4	3	1	6	14	—	—	—	2	2	16
1-2,000 to 1-3,000	2	2	5	3	12	—	—	—	3	3	15
1-3,000 to 1-4,000	3	1	4	7	15	—	—	—	2	2	17
Less than 1-4,000	5	3	0	4	12	—	—	—	—	0	12
Total (1-1500)	14	9	10	20	53	0	0	0	7	7	60
Grand total...	18	10	20	28	76	0	0	5	21	26	102

PART III.—Total Polynuclear White Corpuscles.

Over 3,000 ...	—	—	—	—	0	—	—	3	4	7	7
2,000 to 3,000 ...	1	—	1	—	2	—	—	—	2	2	4
1,000 to 2,000 ...	2	—	2	9	13	—	—	1	7	8	21
500 to 1,000 ...	5	4	5	8	22	—	—	1	1	2	24
250 to 500 ...	4	4	6	7	21	—	—	1	2	3	24
Less than 250 ...	5	1	1	1	8	—	—	—	—	0	8
Total ...	17	9	15	25	66	0	0	6	16	22	88

The Total Leucocyte Count.

In the first part of the table the figures of the total leucocyte counts are shown according to the degree of leucopenia present. The cases are also classed according to the result, the fatal cases being shown in the first column; in the second, those in which the fever continued for some time unabated by treatment, which are returned as "worse;" thirdly, those in which the result was uncertain, owing to the shortness of time under observation; and fourthly, those which improved and were likely to recover, the fever having either stopped or declined to the low, intermittent type, which, I shall show presently, may be accompanied by steady improvement in both the blood and the general condition and weight, and eventually merge into complete recovery of health. Several of the cases entered in the third column as doubtful also showed signs which gave good hope of recovery, but were not long enough under treatment to enable a favourable prognosis being given. It will be seen from the table that while 28 cases either died or got worse, yet an equal number showed signs of improvement, while 20 were classed as "doubtful." On the other hand, among those in which no Leishman bodies were found no case either died or got worse, while 22 showed signs of improvement or recovered, although some of them were clinically typical cachexial fever cases. This is supported by the fact that the parasites may be very few and small in recovering cases, and may only be found at a second spleen puncture. Sometimes they are found by my method of culture after a day or two, although not met with in the original spleen blood films in the course of a careful examination. It is clear, then, that a negative spleen puncture is not certain evidence of the absence of the new parasites, although, on the other hand, it is of very good prognostic import.

Turning to the degree of loss of the leucocytes, we find that in only 4 out of 76 cases showing Leishman bodies were over 3,000 leucocytes present, and 3 of these were complicated by dysentery, phthisis, and pneumonococcus meningitis respectively, while the fourth showed only a very few shrunken parasites; the patient had no fever, and was apparently recovering from a very chronic attack of fever on and off for ten years, with a large and very hard spleen. On the other hand, no less than 15 out of the 26 cases in which no parasites were found showed over 3,000 leucocytes, most of them being malarial cases, while others were probably recovered cases of cachexial fever in which a large, hard spleen remained, while 2 were cases of phthisis with similar hard spleens. These cases chiefly occurred in the autumnal malarial season (when malarial fevers with parasites are extremely common both in the native and European Calcutta hospitals). In a few malarial parasites were found in the peripheral blood, but owing to the considerable enlargement of the spleen it was thought that the patients might also be suffering from cachexial fever, so spleen puncture was performed, while in 3 cases they were found in the spleen blood only.

Next we come to the intermediate degrees of leucopenia in which only from 2,000 to 3,000 white corpuscles were found. Out of 23 such cases 17 showed Leishman bodies, while in only 6 were they not detected. Among the 17 positive cases no less than 10 improved under treatment, while only 3 died or got worse, thus confirming the good prognostic value of relatively slight degree of leucopenia in the disease, which I pointed out in my Oxford paper. Among the 6 cases with similar counts in which no Leishman bodies were obtained by spleen puncture, 2 had spleens enlarged down to the anterior superior spine of the ilium, in 2 it reached to the navel, while it was not noted in 1. The sixth was a malarial case, malignant tertian parasites being found in the spleen, but not in the peripheral blood. Thus at least 4 of them were clinically cachexial fever cases on the way to recovery.

Among the cases showing the most marked degrees of leucopenia—namely, less than 2,000 white corpuscles—55 out of 62 showed Leishman bodies in the spleen, and no less than 23 of them died or got worse under treatment, while only 17 showed any improvement, thus reversing the prognosis obtained from the higher leucocyte count. The mortality was specially high among those which showed the extreme leucopenia represented by counts of 1,000 and less. Of the 7 cases with 2,000 or less leucocytes in which no Leishman bodies were found 5 showed improvement and 2 were doubtful. Five were clinically typical recovering cases of cachexial fever, 1 was doubtful, while 1 was malarial, malignant tertian parasites having been found in the spleen blood.

Taking the table as a whole we find that among the cases in which the new parasite was found in the spleen over 3,000 leucocytes were only found when some complication which might be expected to increase them was present, or the case was recovering; while in those showing 2,000 to 3,000 the prognosis was also comparatively favourable. A leucopenia of still greater degree than the above strongly points to

cachexial fever, although it may also occur in a few cases of true malarial cachexia with marked anaemia.

The Ratio of White Corpuscles to the Red.

Not only are the white corpuscles very much diminished absolutely in cachexial fever and kala-azar, but, as I have already pointed out with regard to both forms of the disease, the leucocytes are decreased in a much greater degree than are the red, so that instead of finding a normal relationship of 1 white to 600 or 700 red we nearly constantly find the ratio much below this point. The data of 102 counts are given in the second part of the table, which, besides showing very similar general results to those derived from the total leucocyte count, also presents some points of special interest. Out of 76 cases in which the new parasites were found in the spleen only 10 showed a ratio of more than 1 white to 1,000 red corpuscles, and 8 of these showed complications likely to have increased the ratio, including dysentery, phthisis, meningitis, and cancrum oris. The remaining two were recovering, having lost their fever, and showed only a few parasites in their spleen blood. On the other hand, 14 out of the 26 cases in which the new parasites were not found by spleen puncture show a similar normal ratio of white corpuscles. Moreover, the three cases in which malarial parasites were found in the spleen blood fall among these, although two of them showed very low total leucocyte counts, a point of the greatest importance, which is supported by the cases of true malarial cachexia given in Table II. Next, in cases showing an intermediate degree of decreased ratio of white corpuscles falling between 1 to 1,000 and 1 to 1,500, we see that in 13 out of 18 the new parasites were found in the spleen blood, while of the negative cases 4 were clinically typical favourable cases of cachexial fever with hard spleens enlarged down to the navel or beyond, while I have no clinical notes of the remaining case. I find, however, on reference to my tables of fever cases in which blood counts have been carried out during the last few years, that a relative reduction of the leucocytes of this degree may occur in typhoid fever, and also, I think, exceptionally in chronic malarial anaemia, so that, although highly suggestive of cachexial fever in a doubtful cases, it cannot be looked on as certainly diagnostic of the latter disease. When we come, however, to the more marked degrees of this change shown in the last four columns of Part II of Table I—namely, from ratios of less than 1 leucocyte to 1,500 red down to less than 1 to 5,000, we find we have a very valuable means of diagnosing cachexial from other fevers. Thus, out of 60 cases the new parasites were found in no less than 53 by spleen puncture, while out of the 7 negative cases 6 at least were clinically typical favourable cases of the disease, while the remaining 1 was probably also of the same nature, although admitted for ascites, a not very rare sequela of the more chronic forms of the affection.

The Total Polynuclears.

The third part of Table I shows the number of polynuclears obtained from worked-out from the total and differential leucocyte counts. The figures show very parallel results with those of the ratio of white to red corpuscles, so need only be very briefly considered, as, in view of the fact that equally valuable results can be obtained from the much quicker and simpler total counts of the red and white corpuscles, it is not of so much practical value as the former, although useful from the prognostic point of view. The only cases with Leishman bodies which showed over 2,000 polynuclears were complicated by meningitis and phthisis respectively. Below that point the great majority of the cases showed the new parasites, the prognosis becoming progressively worse as the number of polynuclears decreased. One malarial case with very marked anaemia, however, showed under 500 polynuclears, although the ratio of white to red was over 1 to 1,000, so that from this point of view the total polynuclear count does not appear to be quite so reliable a diagnostic aid as the simpler estimation of the ratios of the white to the red corpuscles.

The Blood Changes in True Malarial Cachexia.

Now that it has been found that the great majority of the cases hitherto regarded as "malarial cachexia" are actually caused by the new spleen parasite, and not by the malarial organisms, there has been an inevitable tendency to rush to the other extreme and deny the existence of true malarial cachexia with marked enlargement of the spleen. In Calcutta, where, on account of good drainage, but little malaria originates, except on the outskirts, the great majority of cases of chronic fever with very large spleens down to the navel in adults are undoubtedly due to the new parasite, and true chronic malaria is proportionately rare. In the very malarious districts of Dinajpur, however, I found the new parasite in only ten out of thirty large spleens which I punctured, while in five others malarial parasites were detected. Even in Dinajpur the endemic index must be comparatively low unless it differs greatly from that of the closely similarly situated district of Jalpaiguri, where the Malaria Commission found it to be 12 per cent. In order to study true malarial cachexia advantageously a place with a still higher endemic index is necessary, and preferably one in which cachexial fever cases are absent. Such an opportunity I recently met with in the Nowgong district of Assam, thanks to the great kindness of my friend, Dr. Dodds Price. As long ago as early in 1897 Dr. Price, at my suggestion, moved out the uninfected coolies from a line in which nearly half the inhabitants were suffering from kala-azar, with such satisfactory results that among over 500 people, including nearly 100 from the old lines, no case of the disease has appeared in the last eight years, during which time they have been under his charge. More recently several other infected lines have been cleared out in the same way, so that at the time of my recent visit I was able to examine the children in different lines which had been entirely free from the disease for varying numbers of years. In the line originally moved and longest free from the disease I found malarial parasites in 18 out of 20 children, giving an endemic index of 90 per cent. In another line, which had not been moved and in which kala-azar had been very bad, and was still present, an equal number of children gave an endemic index for malaria of 80 per cent. All three forms of malarial parasites were found, quartans and malignant tertians being most commonly met with. These data are of great interest from two points of view. In the first place, they show that the very gardens on which I examined so many cases of kala-azar eight years ago present one of the highest malarial fever-rates in India, and this accounts for the frequency with which I found malarial parasites in cases of kala-azar and the uniformity with which the tissues of those dying of the epidemic disease showed the pigment characteristic of malaria.

In the second place, the fact that both the infected and the uninfected lines each showed a very similar degree of malaria completes the proof that malaria is not an essential factor in the production of kala-azar, although it may well act as a predisposing cause by decreasing the resisting power of the patient, and especially by reducing the number of the leucocytes. An examination of a number of cases of kala-azar in the light of my recent studies of cachexial fever in Lower Bengal has also fully confirmed the opinion I expressed in my original report on the former disease, namely, "In the later stages the disease presents only the usual symptoms of malarial cachexia, and even then, individually considered, it is impossible to distinguish them from chronic malaria, as can be seen at a glance by a comparison of the photographs of kala-azar cases opposite pp. 33 and 57, with those of ordinary malarial cachexia as seen in Sylhet, where there is no kala-azar." I did not, however, foresee that the disease known as "malarial cachexia" would prove to be not malarial at all, although in my conclusions with regard to the nature of the disease I wrote: "It is, however, open to anyone to say that there is something in addition to malaria, which I have not discovered, but which accounts for the spread of the affection." At the present time the segregation measures have nearly eradicated the disease from the tea-garden lines, in spite of the yearly importation of susceptible material, while now that the disease has also markedly declined in the Nowgong district, and its spread further east has been largely checked, the epidemic appears to be nearly at an end, and the cases now seen differ only from the endemic form of Bengal—itself the remains of the great Burdwan epidemic of the Sixties and Seventies—in its somewhat greater virulence and the larger number of parasites in the spleen blood usually met with in kala-azar cases.

In addition to working out the endemic index in an infected and in an uninfected line, the children under 10 were examined for enlargement of the spleen in five coolie lines, three of which were new ones and free from kala-azar, one was a badly-infected one, and the fifth only very slightly infected. The spleen-rate was very similar in each, both as to the percentage of enlarged spleens and also the proportions of different degrees of enlargement. In all, 232 children were examined, and the organ could be felt below the ribs in 84.92 per cent. of them. The degrees of enlargement are also of interest, especially in the uninfected lines which were free

TABLE II.—*Blood Changes in True Malarial Cachexia.*

No.	Sex.	Age.	Spleen Down to.	Malaria Parasites.	Red Corpuscles.	White Corpuscles.	Ratio of White to Red.	Total Poly-nuclears.	Poly-nuclears.	Lympho-cytes.	Large Mono-nuclears.	
									%	%	%	
1	F.	6	Below navel	Malignant tertian	4,800,000	5,500	1-873	1,870	50	34	15	1
2	M.	8	Navel	Quartan	3,910,000	6,125	1-637	2,817	46	39	12	4
3	M.	8	4	*Nil*	2,035,000	4,250	1-477	2,550	60	23	8	9
4	F.	1	Below navel	Malignant tertian	2,350,000	2,625	1-895	895	34	52	14	1
5	F.	1½	4	Benign tertian	3,790,000	4,000	1-948	1,536	38	28	10	24
6	F.	3	Below navel	Quartan	4,370,000	5,500	1-795	2,750	50	37	12	1
7	M.	2⅔	Below navel	Quartan	2,170,000	3,250	1-667	2,420	44	30	9	17
8	M.	5	Navel	Quartan	4,670,000	7,125	1-655	3,491	49	34	12	5
9	F.	6	Navel	*Nil*	2,520,000	4,625	1-544	2,578	56	28	11	5

from kala-azar, which included 140 children. Of these, no enlargement was found in 13.6 per cent., the organ was just felt in 33 6 per cent., it extended 2 in. below the ribs in 27.1 per cent., and 4 in. below in 17.1 per cent., and in 8.6 per cent. it reached to the level of the navel or below it. It is clear, then, that in a highly malarious district a very considerable frequency and degree of enlargement of the spleen is found in places which are, and have been for years, quite free from the disease due to the Leishman bodies, and hence, no doubt, produced by malaria alone. Twenty of the children who showed the largest spleens, extending to 4 in. or more below the ribs, were more closely examined, their red and white corpuscles enumerated, and differential counts of the white corpuscles made, in order to see whether the blood changes differed in any constant way from those met with in cachexial fever. Many of them were thin and anaemic, presenting undoubted clinical symptoms of true malarial cachexia, while the figures in Table II, of 9 consecutive cases from the lines which are free from kala-azar, show that in several of them the red corpuscles had fallen to only about half the normal numbers. Most of them also showed malarial parasites in their peripheral blood at the time of examination. The white corpuscles were also markedly reduced in most of the cases, being as low as 2,625 in one (No. 4), but the column showing the ratio of the white to the red corpuscles shows that both are equally reduced, and in no case of the whole 20 examined was the ratio as low as 1 white to 1,000 red. In this respect these true malarial cachexia cases are in marked contrast to what is met with in all uncomplicated and active cases of cachexial fever, as I have shown in the earlier part of this paper, thus confirming the conclusion previously come to from the above analysis of over 100 spleen puncture cases in the Calcutta hospitals, that the marked decrease in the ratio of the white corpuscles to the red is peculiar to cachexial fever and to kala-azar—in which disease I drew attention to this change eight years ago—and this simple method will enable the diseases due to Leishman bodies to be differentiated in the great majority of cases from true malarial cachexia, from which they are not infrequently indistinguishable by an ordinary clinical examination—a matter of considerable practical importance. Moreover, this change is nearly always well marked when patients first come to hospital with the disease, although, as they usually give a history of intermittent fever on and off for from two to six months, I am not yet able to state how early in the disease the change occurs, although in Case 7 of Table III it was found within three weeks of the onset of the fever.

FISH AND TRYPANOSOMES.

I may also mention here that while in Assam I examined a large number of fish for trypanosomes from both infected and uninfected lines, and found them present in both series in nearly equal numbers in the same kinds of fish, so that I was unable to confirm Bentley's statements on this point. Moreover, I have failed to infect fish with either Leishman bodies or the flagellated forms derived from them by culture.

THE TREATMENT OF THE LEUCOPENIA OF CACHEXIAL FEVER AND KALA-AZAR.

In my report on kala-azar of 1897 I pointed out that the yellow marrow of the shafts of the long bones is always converted to a large extent into red marrow in fatal cases, and, looking on this as an attempt on the part of the system to repair the blood, I tried the administration of red medulla tabloids in cases of kala-azar, with favourable results in several cases. Recently, thanks to the kindness of my colleagues at the European General Hospital, I have been able to closely watch a series of cases in which they have tested this treatment, combined with steady perseverance with quinine to keep the fever down as far as possible to the low intermittent type. It is too early to speak decisively as to the exact value of this method, but all who have seen the cases are convinced that it has done good in several, although it has failed in others, while some interesting light has been thrown on certain features of the course of the disease, which are not without practical importance. The results in all the cases treated for any considerable length of time, whether successfully or otherwise, are shown in Table III, the dates on which the blood counts were done being noted and the condition of the fever and of the patient generally at the same time entered in the last column. In the cases marked (*) Leishman bodies were found by spleen puncture, but in No. 5 no parasites were obtained in this way, although the case was a very typical one of cachexial fever, but the puncture was done after the cancrum oris had set in and he was beginning to improve—a significant point, as will be seen presently. In the other cases spleen puncture was not performed, the patients being European women and children, and the clinical characters of the disease being beyond question.

The results have been somewhat variable as a whole, but one point stands out clearly—namely, that whenever the fever assumes the remittent type both the blood and the general condition of the patient steadily and often rapidly deteriorate, while, on the other hand, prolonged intermittent fever, even of several months' duration, is not incompatible with steady improvement, both in the blood, especially in the number of the white corpuscles and their ratio to the red, and also in the general condition of the patient, as shown by a steady and marked increase in strength and weight and a reduction in the emaciation which is so characteristic of the disease. This is of great practical importance, for, as I have maintained for years against the nearly universal opinion of other writers on tropical medicine, quinine has a very material action on the fever in these cases, reducing it from the dangerous remittent type to an intermittent one, which may allow of improvement in the general health, and I now find that when the leucocytes have increased up to a certain point under the bone marrow treatment the fever has then stopped in several cases, and recovery ensued. It will be well to illustrate these points as briefly as possible by reference to some of the cases given in Table III.

First, as regards the fatal cases. No. 1 improved considerably in hospital, but left before she was nearly completely recovered. A few weeks after she was readmitted suffering from pneumonia, and died in a few hours. Had she continued under treatment she might very well have recovered. The other two fatal cases—Nos. 11 and 13—were under treatment for long periods without ever showing any definite improvement, the latter suffering from an acute attack of herpes zoster, followed by deep ulceration of each patch, apparently due to the lowered resistance of the tissues to bacterial invasion. Unfortunately the supply of bone-marrow tabloids ran out in Calcutta, as well as in other large Indian towns which were written to for them, and for some three weeks these two patients were without them, during which time they got worse and both died. This may, however, have been only a coincidence. Next, we have Case 4, who cannot, on the whole, be said to have materially improved, although for a time she did so, the fever becoming much less and the leucocytes markedly increasing. Recently, however, the remittent type of fever has reappeared, and she has gone back again. The case illustrates very well the relationship of remittent fever to a progressive deterioration of the blood and general condition and the improvement during low intermittent fever.

Table III.—*Effects of Bone Marrow and Quinine Treatment on the Blood.*

No.	Sex.	Age.	Date Examined.	Red Corpuscles.	White Corpuscles.	Ratio of White to Red.	Total Polynuclears.	Polynuclears.	Lymphocytes.	Large Mononuclears.	Type of Fever.	General Condition.
								%	%	%		
*1	F.	21	30- 4	3,485,000	875	1-3,970	481	55	36	9	Intermittent to 101	
			10- 5	3,510,000	1,375	1-2,553	—	—	—	—	,,	Improving.
			6- 6	3,360,000	1,125	1-2,986	—	—	—	—	,, to 100	Better. Left hospital; returned with pneumonia. Died.
*2	M.	4	6- 5	3,205,000	875	1-3,885	346	42	48	8	Intermittent	Spleen very large.
			14- 6	3,970,000	1,875	1-2,184	503	27	63	10	Low fever only	Improved.
			8- 9	4,650,000	5,750	1- 809	2,645	47	47	4	No fever two months	Fat and well.
*3	F.	16	24- 6	2,750,000	750	1-3,666	142	19	54	26	Intermittent and low remittent	
			8- 9	2,680,000	1,375	1-1,949	560	40	44	16	Intermittent to 101	Improved.
			19-11	3,410,000	4,375	1- 779	2,450	56	29	15	No fever one month	Much better.
			14-12	3,820,000	5,000	1- 764	2,850	57	30	13	No fever	Gained weight, nearly well.
*4	F.	23	11- 7	3,000,000	750	1-4,120	300	46	38	22	High remittent	
			13- 9	2,890,000	3,250	1- 890	2,372	73	22	5	Low intermittent	Improved.
			21-11	3,780,000	3,000	1-1,260	—	—	—	—	Intermittent 101	No change.
			14-12	3,920,000	1,750	1-2,240	—	—	—	—	Remittent	Worse.
5	M.	19	12- 7	3,390,000	875	1-3,873	—	—	—	—	Intermittent 101	Cancrum oris.
			22-11	2,880,000	6,125	1- 469	—	—	—	—	No fever	Cancrum oris healing.
6	F.	6	15- 7	4,080,000	1,375	1-2,967	330	24	61	15	High remittent	
			31- 8	2,335,000	750	1-3,113	360	48	34	18	,, all through	Worse.
			17-11	3,080,000	2,875	1-1,071	1,380	48	39	13	Fever, low intermittent	After cancrum oris.
7	F.	7	15- 7	5,270,000	4,750	1-1,240	2,375	50	29	17	Double remittent	Much improved.
			31- 8	3,670,000	2,875	1-1,274	1,292	58	52	24	Remittent	Worse.
			17-11	4,550,000	5,375	1- 854	2,795	52	43	5	*Nil* or low, intermittent	Improved greatly.
8	F.	13	3- 8	2,690,000	750	1-3,578	142	19	59	22	Intermittent	Spleen very large.
			10- 9	3,490,000	1,250	1-2,792	431	34	52	24	,,	Improved.
			17-11	3,640,000	3,250	1-1,201	1,820	56	38	8	Had dysentery	Improving again.
9	F.	35	5- 8	3,880,000	1,375	1-2,822	1,072	78	16	6	Remittent	
			21- 9	3,830,000	2,000	1-1,915	—	—	—	—	Low intermittent	Improved.
			5-10	4,500,000	2,125	1-2,117	1,764	83	13	4	Normal	,,
			21-11	3,800,000	1,375	1-2,894	—	—	—	—	Remittent	Worse.
			14-11	4,390,000	2,125	1-2,066	1,509	71	17	12	No fever one month	Much better.
10	M.	5	13- 8	2,950,000	2,875	1-1,026	747	35	40	34	High remittent	Getting worse.
			18-11	2,590,000	5,250	1- 429	1,877	35	46	19	Intermittent	Much improved.
11	F.	31	30- 8	3,800,000	2,875	1-1,322	1,358	48	38	14	Double remittent	
			5-10	4,080,000	2,500	1-1,632	1,600	64	25	11	Low intermittent	Improved slightly.
			22-11	4,360,000	2,625	1-1,675	—	—	—	—	Intermittent to 102	No change. Died December 12th.
*12	M.	37	28- 9	2,650,000	1,375	1-1,927	611	45	37	18	Intermittent	Fair condition.
			4-10	4,680,000	4,000	1-1,170	2,288	57	29	12	No fever last few days	Much improved.
*13	F.	20	21- 9	4,070,000	1,875	1-2,179	1,311	71	23	6	Low intermittent	
			21-11	3,070,000	1,625	1-1,874	—	—	—	—	,, ,,	Sloughing herpes zoster. Died in Dec. with diarrhoea and cancrum oris.

* Leishman bodies found in the spleen blood.

Thirdly, we have cases which show slight improvement only, including Nos. 6 and 8. The former is a most remarkable case, illustrating the extraordinary way in which the most desperate cases may improve. The child was very bad on admission, and in spite of all treatment high remittent fever, often of the double type, continued unabated, and at length cancum oris set in, and directions were actually given for the spleen to be punctured after her death, in order to look for Leishman bodies. Fortunately the temperature fell, and in a few days she was toddling about the ward, and her blood—especially the number and ratio of the leucocytes—was found to have markedly improved. The prognosis is still bad, but by no means hopeless, as I know from my Assam experience that no case need be despaired of—a remarkable feature which may be overlooked in hospital practice, and thus the disease be considered to be more frequently fatal than it really is. Case 8 also shows considerable improvement in the blood; the girl has been much weakened by dysentery, but is once more on the mend.

The remaining cases have either markedly improved or actually recovered. Thus Nos. 5, 7, 9, and 10 have either remained free from fever altogether for some time, or shown only low remittent type, while all of them show marked improvement in the blood conditions, and especially in the leucocytes. No. 5 is another example of a remarkable improvement in the blood and decline of the fever following cancrum oris. Indeed, this complication appears to be of the "kill or cure" description, for although commonly fatal, especially if not accompanied by any increase in the small number of leucocytes present—a relative leucocytosis—then death usually ensues, and the spleen is found to be full of parasites. If, however, a considerable degree of relative leucocytosis occurs, then the fever may cease and the patient recover, and no parasites be found by spleen puncture, as in Case 5. Whether it will prove possible to cure the fever by producing a more active increase of the leucocytes than by the slow, if sound, bone-marrow treatment, is a problem which is now engaging my attention. No. 7 is of interest as being a rare example of the disease coming under observation at a very early stage, being thought at first to be typhoid, although the occurrence of a well-marked double remittent type of fever made me suspect cachexial fever, which has been fully confirmed by the subsequent course of the disease, and the repeated negative result of the serum test. The remittent type of fever persisted, with one intermission, for over three months, but at length the temperature fell, and a rapid improvement in both the blood and the general condition ensued. It is noteworthy that the ratio of white to red corpuscles was below 1 to 1,000 very early in this case. No. 9 shows very clearly the ups and downs of the leucocytes and general state, with the falls and rises of the temperature curve, but she has now been free from fever for a month, and has gained 9 lb. in weight. Lastly, Nos. 2, 3, and 12 show recoveries, and illustrate the progressive increase in the leucocytes, and especially the polynuclears, the ratio of the white to the red corpuscles, and improvement in the general condition. No. 3 is of special interest, as for five months she was never free from intermittent fever, running up to from 100° to 102° F., yet during that time she improved most remarkably, on the quinine and bone marrow treatment, both in strength and in the number of the leucocytes, and when the latter had reached a fair figure the fever stopped, and she has now gained a good deal of weight, and appears to be almost well, being able to walk several miles. No. 12 showed a similar improvement all round at a time that intermittent fever was continuing, and the leucocytes, and especially the polynuclears, had increased about threefold on re-examination only a few days after the fever finally ceased, so that the improvement must have taken place during the continuance of the fever as in Case 3. No. 2 is the most complete recovery of the series in spite of an enormous spleen, and his low age also being very unfavourable.

If we may judge by Major Donovan's statement that almost every case admitted to his wards in Madras died or went out worse than they came in, the above results may certainly be regarded as highly favourable. For reasons already mentioned, however, I think he takes much too gloomy a view of the prognosis. It is true that in the epidemic form of the disease on Nowgong tea-gardens in Assam before 1897 the mortality of 200 cases worked out at 96 per cent., but that was at the height of the epidemic. Dr. Dodds Price has very kindly worked out the results of 500 cases treated by him in

certain gardens since 1898, and he finds no less than 132, or 26.4 per cent., recovered completely and permanently. It is possible that the more favourable results obtained at the Calcutta European Hospital and by Dr. Price in Assam may be due to another factor, for in view of what has been said above as to marked improvement taking place as long as only low intermittent fever is present, and the fact that in Calcutta it has been repeatedly found that the temperature runs up to the remittent type the moment quinine is left off (a point which will shortly be illustrated by Captain Clayton A. Lane, I.M.S.), there is good reason for believing that the much more favourable results of Dr. Price and myself than those reported by Major Donovan are causally related to the firm belief in, and the practice of, giving large doses of quinine in cachexial fever and kala-azar by the former, in opposition to the view of Major Donovan and others that quinine is useless in even the milder endemic form of the affection. At any rate, it can hardly be maintained that quinine does any harm, when it is considered that 60 gr. and upwards have frequently been given daily for long periods in some of the favourable cases recorded above, with much better results than any yet reported by those who deny the value of the drug; so that the proof afforded above, that even a reduction in the fever curve makes all the difference between deterioration and improvement, appears to me to render it inadvisable to deny these unfortunate patients the benefit conferred by quinine, combined with the administration of red medulla tabloids, or their equivalent in uncooked marrow mixed with other food to render it palatable.

Finally, I have to express my great indebtedness to my colleagues Lieutenant-Colonel G. F. A. Harris and Major F. J. Drury, the Physicians of the Medical College Hospital, and to Captains Clayton A. Lane and R. P. Wilson, of the European General Hospital, all of the I.M.S., for their kindness in allowing me to examine and make use of their cases.

CONCLUSIONS.

1. A very marked decrease in the leucocytes is always found in uncomplicated cases of cachexial fever, and when they number below 2,000 per c.cm. this is almost diagnostic of the disease, but may rarely occur in true malarial cachexia.

2. In cachexial fever the white corpuscles are reduced to a greater degree than the red, so that the ratio falls below 1 to 1,000 in all uncomplicated progressive cases. This is rarely so in true malarial cachexia, while a reduction in the ratio to below 1 to 1,500 appears to be quite diagnostic of cachexial from other Indian fevers.

3. The most marked degrees of reduction of the leucocytes, and especially of the polynuclears, is of bad prognostic import, and vice versa.

4. Red narrow tabloids are of great value in increasing the leucocytes, and this increase may take place during the continuance for months of intermittent fever, and be then followed by cessation of the fever and complete recovery.

5. High remittent fever is accompanied by progressive deterioration of the blood and general condition, but it may be often to a large extent reduced to the less injurious intermittent form by continued large doses of quinine, combined with red marrow. The best results yet reported have been obtained by those who carry out vigorous quinine treatment.

REFERENCE.

[1] *Quart. Jour. of Micros. Science*, November, 1904.

THE EXPERIMENTAL TRANSMISSION OF MEDITERRANEAN FEVER.

BY

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(Communicated by the DIRECTOR-GENERAL R.N.)

[PRELIMINARY NOTICE.]

It having been suggested to us, by Professor Ronald Ross, that Mediterranean fever is possibly conveyed from person to person by the mosquitos *Stegomyia fasciata* or *Culex pipiens*, and bearing in mind the work of the Commission of the United States Army on yellow fever,[1] we have made some experiments in the hope of ascertaining the true nature of the transmission of this disease.

Experiment 1.—Transmission by Direct Contact, Fomites, etc.

A case of Mediterranean fever was treated in the sick berth of a ship for a period of one month, while she was at sea or when in captivity. anchored in open roadsteads. The fever was fairly severe, the serum reaction was positive, and the micrococcus melitensis separated from the blood of the patient.

He was nursed by three non-immunes, who took no special precautions to avoid contracting the disease, and who twice slept in the bedclothes which had been used by the patient. The disease was not conveyed to these non-immunes.

This experiment was then repeated in another ship with another but more severe case of Mediterranean fever, and nursed by other non-immunes. The result was the same as before.

In both these cases the Mediterranean fever was obviously contracted before embarkation. No cases of the disease had occurred before in the ships and none were contracted afterwards.

Experiment 2.—Transmission by Inhalation, Infected Dust, etc.

The urine of a case of Malta fever, passed on the fifth day of the disease, with fever of 103.8° F., was mixed with some dust, making a thick paste; part of this was allowed to dry slowly in the shade for five days and powdered.

The dust was then inhaled, sniffed up the nostrils, and a considerable quantity swallowed by two non-immunes (E. H. R. and Mr. C.). The remainder of the infected dust was kept for six days, then dried in the sun and powdered, and this also inhaled, sniffed up the nostrils, and swallowed by the same non-immunes. The disease was not conveyed by these means.

A living culture of micrococcus melitensis, grown on agar for seven days, was spread on a glass plate, it being kept moist meanwhile, and was inhaled for one hour by one of us (E. H. R.); the culture was then allowed to dry, and finely powdered; this was then inhaled for three hours, and ultimately sniffed up the nostrils, and some of it swallowed by the same non-immune. The disease was not contracted by him.

Experiment 3.—Transmission by Infected Water.

Ten ounces of the urine of a case of Malta fever, in the sixth week of the disease, was mixed with five gallons of ordinary drinking water; a tumblerful of this mixture was then drunk by two of us (E. H. R. and G. M. L.). When the urine was passed the patient's temperature was 102.4° F., and when mixed with drinking water, an hour later, was neutral to litmus. The disease was not contracted by either of us.

Experiment 4.—Transmission by Mosquitos.

Two female mosquitos of the species *Stegomyia fasciata*, Fabricius (var. *Culex mosquito*, R. Desvoidy), and one female *Stegomyia pseudotaeniata* (Giles), were allowed to bite a patient suffering from Mediterranean fever in the third week of the disease, whose temperature at the time was 103° F. The mosquitos were then allowed to bite the two non-immunes (E. H. R. and Mr. C.) alternately on the sixth, twelfth, seventeenth, and twentieth nights after.

These same mosquitos were then reinfected from a fresh case of Malta fever, in the sixth week of the disease—temperature 101.6° F.—and again allowed to bite the same two non-immunes alternately as before, twenty-four hours, fourth, sixth, eighth, eleventh, thirteenth, and fifteenth days after. Two of these mosquitos then died; the remaining one, a *Stegomyia fasciata*, was then again reinfected from a fresh case of Malta fever, with a temperature of 103° F., who was in the eleventh week of the disease. This mosquito then fed on the blood of Mr. C. twenty-four and again forty hours after. The mosquito then died.

The disease was not conveyed by these means.

The possibility of the transmission being due to mosquitos infected in the early days of the disease having been suggested, another *Stegomyia* was allowed to distend herself with the blood of a very severe case on the second day and again on the eighth day of the illness, the patient's temperature on the two occasions being 102.4° F. and 103.2° F. respectively. This mosquito was then allowed to bite two other non-immunes—G. L. M. and Mr. D.—alternately on the third, sixth, tenth, twelfth, fourteenth, sixteenth, and seventeenth days afterwards.

The disease was not contracted by these non-immunes either.

Similar experiments have been attempted with other gnats—*Culex pipiens* (Linneus), *Culex fatigans* (Wiedermann), and the sea-water bred species, *Acartomyia zammitii* and *Theobaldia spathepalpis* (Rondani), but these have up to the present failed owing to the difficulty of making these species feed on blood

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